REMARKS

Reconsideration of this application is respectfully requested.

Claims 1-37 were pending in this application. Claims 19-37 have been cancelled without prejudice to the filing of continuation applications. Claims 1, 12-15 and 18 have been amended for clarification. Claims 1-18 are now pending in this application. No new matter has been added to the application as a result of the present amendment.

Turning to the Office Action, the claims are subject to a restriction requirement; the drawings are objected to as informal; parts of the application are objected to for containing uncapitalized trademark names, for containing sequence listings that are not accompanied by a sequence identification number, for containing an unidentified abbreviation, and for including full sequences in the claims where only a sequence identification number is necessary; claims 1-10, 13, and 16-18 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite; claims 1-10 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Rasche et al., *Arzneimittel-Forschung* 25(1), 110-116 (1975) ("Rasche")[1]; claims 3-10 stand rejected under 35 U.S.C. § 103 as being unpatentable over Rasche in view of the state of the art; claims 13, and 16-18 stand rejected under § 103 as being unpatentable over Delaria et al., *J. Biol. Chem.* 1997, 272(18), 12209-12214 ("Delaria") in view of the state of the art as exemplified by Rasche, Fritz et al., U.S. Patent No. 5,407,915 ("Fritz"), and O'Riordan et al., *Am. J. Respir. Crit. Care Med.* Vol. 155, pp. 1522-1528 (O'Riordan"); and claims 1-10, 13, and 16-18 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-10 and 15-18 of copending application number 09/441,966.

Applicants respectfully request that the Office hold the objection to the drawings in abeyance pending allowance of the claims. Applicants further request that the Office hold the obviousness-type double patenting rejection in abeyance pending allowance of the instant claims, at which time a Terminal Disclaimer will be filed. Under the present amendment, the specification has been amended to capitalize trademark names; to define the abbreviation "AMC"; and to add sequence identification numbers; and the claims have been amended to remove full sequences where a sequence identifier is provided. In view of these amendments, Applicants respectfully request withdrawal of the objections to the specification and the claims. The remaining rejections are addressed below.

[1] An English translation of Rasche is enclosed with the accompanying Information Disclosure Statement.

The Restriction Requirement

Claims 1-36 are subject to a restriction requirement. Applicants affirm the election of Group I, claims 1-18, and the species of SEQ ID NO: 52, which were provisionally elected during a telephone conversation between the Examiner and Applicants' undersigned representative.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1-10, 13, and 16-18 stand rejected under § 112 as indefinite. The Office contends that claim 1 is indefinite because the phrase "subject in need of such a treatment" fails to set forth the metes and bounds of the patent protection sought. Claim 1 has been amended to replace this phrase with "subject with mucociliary dysfuncion." Support for this amendment can be found in the specification, for example, on page 8, lines 16-17.

Claim 10 stands rejected on the grounds that the phrase "physiologically buffered solution" fails to set forth the metes and bounds of the patent protection sought. Under the present amendment, "physiologically" has been removed from the phrase, since this word already appears in the base claim. Applicants respectfully submit that the meaning of "buffered solution" was well known to the person of ordinary skill in the art at the time this invention was made. Claim 10, as amended, is therefore not indefinite.

Claim 18 stands rejected as indefinite on the grounds that the phrase "according to the amino acid sequence of native human placental bikunin" does not clearly set forth the metes and bounds of the patent protection sought. Under the present amendment, claim 18 has been amended to refer to a specific SEQ ID NO. rather than the term "native human placental bikunin." Support for this amendment can be found in the specification, on page 22, line 30, to page 23, line 17.

Applicants respectfully submit that under the present amendment, the alleged indefineness has been removed from the claims. Accordingly, withdrawal of the § 112, second paragraph, rejection of claims 1, 10, and 18, and dependent claims 2-9, 16, and 17, is respectfully requested.

Rejection Under 35 U.S.C. § 102

Claims 1-10 stand rejected as being anticipated by Rasche[2]. The Office contends that Rasche teaches the use of a Kunitz-type serine protease in a pharmaceutical composition in the treatment of obstructive bronchitis. Applicants respectfully traverse this rejection.

As a general rule, for prior art to anticipate under section 102, every element of the claimed invention must be identically disclosed in a single reference. *Corning Glass Works v. Sumitomo Electric*, 9 USPQ2d 1962, 1965 (Fed. Cir. 1989). The exclusion of a claimed element, no matter how insubstantial or obvious, from a reference is enough to negate anticipation. *Connell v. Sears, Robuck & Co.*, 220 USPQ193, 1098 (Fed. Cir. 1983). Applicants respectfully submit that Rasche does not disclose the use of a Kunitz domain serine protease inhibitor for accelerating the rates of mucociliary clearance as presently claimed. Therefore, claims 1-10 are not anticipated by Rasche.

Rasche merely relates to the administration of Aprotinin (infusion or inhalation) to subjects who suffer from moderate to severe chronic obstructive bronchitis. The document measures 24-hour sputum volume as well as pulmonary function as a function of total resistance and intrathoracic gas volume. The authors also analyzed sputum obtained 16 hours after Aprotinin administration and looked specifically at the total dry weight of serous and mucous fractions, total protein content, alpha 1 – anti-trypsin concentration, and fibrinolytic activity. The authors then stated the following:

> Inhalation of the product produced an impressive drop in the average airways resistance which was very high in some of the patients we treated, in the first phase of inhalation with all the inhibitor concentrations administered, which can be explained by both objectively and subjectively improved expectoration by the patient and by a generally observed liquefaction of the initially very viscous sputum.

[2] Applicants note that the journal citation indicated by the Examiner does not correspond to the Rasche reference. Specifically, the Examiner cites *Medizinische Klinik*, 72(5), 144-160 (1975) as the journal citation for Rasche and refers to this reference as being listed as reference number 7 in an IDS (paper 16). However, the Rasche reference cited in Applicants' IDS carries the journal citation *Arzneimittel-Forschung* 25(1), 110-116 (1975). Applicants', therefore, presume that the 102 rejection is based on the Rasche reference having the citation *Arzneimittel-Forschung* 25(1), 110-116 (1975).

See Rasche at page 116, section 4. Discussion paragraph 3. A disclosure of a drop in airway resistance and liquefaction of viscous sputum, however, is not a disclosure of a method for accelerating mucociliary clearance as presently claimed. Rasche does not disclose accelerated rate of mucociliary clearance. Because Rasche does not disclose every element of the claimed invention, the claims are not anticipated by Rasche. Withdrawal of the § 102 rejection of claims 1-10 based on Rasche is in order and is respectfully requested.

Rejections Under 35 U.S.C. § 103

Claims 3-10 stand rejected as being unpatentable over Rasche in view of the state of the art. The Office contents that Rasche provides the motivation for using aprotinin compositions for the treatment of lung conditions and that it would have been *prima facie* obvious to one of ordinary skill in the art to formulate aprotinin in a composition appropriate for administration to human lungs. Applicants respectfully traverse this rejection.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, USPQ2d 1438 (Fed. Cir. 1991). Applicants respectfully submit that one skilled in the art would not have arrived at Applicants' claimed invention based on the teachings of Rasche and the state of the art.

As discussed above, Rasche does not disclose accelerated rate of mucociliary clearance. Furthermore, the observations in Rasche discussed above do not suggest an accelerated rate of mucociliary clearance in the subjects studied. Indeed, Rasche states: "Whether a therapy applying the addition of protease inhibitor is reasonable in the long run in chronic diseases ***cannot*** yet be concluded from these investigations." (Emphasis added). See Rasche at page 116, section 6. This disclosure may be considered as ***teaching away*** from using protease inhibitors for treatment of chronic disease, let alone accelerating mucociliary clearance.

Since Rasche does not suggest an accelerated rate of mucociliary clearance by administering a composition comprising a Kunitz-type serine protease inhibitor, the combination

of Rasche with the state of the art does not teach or suggest Applicants' claimed invention. Accordingly, claims 3-10 are not obvious over Rasche in view of the state of the art, and withdrawal of the § 103 rejection of these claims is in order and is respectfully requested.

Claims 13 and 16-18 stand rejected under § 103 as being unpatentable over Delaria in view of the state of art as exemplified by Rasche, Fritz, and O'Riordan. The Office states that Rasche provides the motivation to develop methods of treatment for a lung condition characterized by improper mucociliary clearance, that Fritz provides the motivation to use human proteins having low molecular weight such as bikunin, and that Delaria provides the motivation to use placental bikunin expressed in mammalian cells in a pharmaceutical composition. The Office then concludes that it would have been obvious to one of ordinary skill in the art "to formulate the glycosylated human protein of SEQ ID NO: 52 taught by Delaria et al. in a pharmaceutical composition by well known methods in the art such as those taught by Fritz et al. and use the composition in a method to treat a condition related to the impairment of mucocilliary clearance similar to that taught by Rasche et al." See Office Action, page 7. Applicants respectfully traverse this rejection and respectfully submit that the Office is improperly engaging in hindsight reconstruction based on Applicants' disclosure.

The Federal Circuit has repeatedly noted: "it is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious. This court has previously stated that '[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.'" *In re Fritch,* 23 USPQ2d 1780, 1784 (Fed. Cir. 1992), citing *In re Fine,* 5 USPQ2d 1596, 1600 (Fed. Cir. 1988); *see also In re Gorman,* 18 USPQ2d 1885, 1888 (Fed. Cir. 1991). The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination and there must be a suggestion or motivation in the reference to do so. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990); (MPEP 2143.01). There is no suggestion or motivation in Delaria, Rasche, Fritz, or O'Riordan to combine these references in the manner suggested by the Office.

Delaria describes an investigation of various inhibitory properties of recombinant placental bikunin1-170 and both of its synthetically prepared Kunitz domains. Delaria, abstract and page 12209. These proteins were found to inhibit a number of serine proteases, such as

plasma and tissue kallikreins, plasmin and factor XIa, which are involved in the intrinsic pathway of blood coagulation and fibrinolysis. Delaria, page 12209 and 12212. As noted by the Office, "Delaria et al. do not teach the use of bikunin1-170 in the treatment of any diseases or conditions." Office Action, page 7. Applicants further note that Delaria makes no mention of mucocilliary clearance, or the use of Kunitz-type serine protease inhibitors in the acceleration of mucocilliary clearance, as claimed by Applicants.

Fritz relates to low molecular weight genetically modified Kunitz-type inhibitors, having proteinase inhibitory activity, and their pharmaceutical preparations. Fritz, col. 1, line 66, col. 2, lines 47-65, col. 4, line 37. Fritz's inhibitors may be capable of inhibiting serine proteases such as pancreatic and granulocytic elastase, cathepsin G or plasma kallikrein. Fritz, col. 1, lines 11-22. Fritz further indicates that potent inhibitors of, for example, neutrophil elastase, could be obtainable by specific genetic modification of the protease's inhibitor. Col. 2, lines 37-44.

Fritz adds nothing to Delaria except for Fritz's disclosure of pharmaceutical preparations of serine proteinase inhibitors and the possibility that inhibitors genetically modified as disclosed by Fritz could be effective against neutrophil elastase. However, a disclosure of genetically modified Kunitz-type inhibitors that potentially inhibit neutrophil elastase is not a disclosure of a method for accelerating mucociliary clearance, as presently claimed. Fritz, like Delaria, makes no mention of mucocilliary clearance, or the use of Applicants' claimed Kunitz-type serine protease inhibitors in the acceleration of mucocilliary clearance. In addition, there is no suggestion or motivation in either Fritz or Delaria that would lead the skilled artisan to combine the references. Further, even if the references are combined, the combination would not disclose a method for accelerating mucociliary clearance, as presently claimed.

O'Riordan reveals that neutrophil elastase may contribute to acute antigen-induced mucocilliary dysfunction. O'Riordan, abstract. Although O'Riordan generally concludes that elastase inhibitors may be useful in protecting against mucocilliary dysfunction, O'Riordan does not contain any specific teachings regarding such inhibitors. Thus, there is no teaching or suggestion in O'Riordan that the Kunitz-type serine protease inhibitors may be useful in accelerating mucociliary clearance.

As discussed above, Rasche relates to the administration of Aprotinin to subjects who suffer from moderate to severe chronic obstructive bronchitis. Rasche does not disclose accelerated rate of mucociliary clearance and appears to ***teach away*** from using protease

inhibitors for treatment of chronic disease in general.

Applicants respectfully submit that the suggestion or motivation to combine Delaria, Fritz, O'Riordan and Rasche is completely absent from the references. Further, Rasche's teaching away from using protease inhibitors for treatment of chronic disease would lead the person of skilled in the art in a direction away from Applicants' claimed invention. The Office appears to have used Applicants' disclosure as a template to piece together the teachings of the prior art. As noted above, such hindsight reconstruction is improper. For these reasons, withdrawal of the 35 U.S.C. § 103 rejection of claims 13 and 16-18 is in order and is respectfully requested.

The Schmidt Reference

During a telephone converstation between the Examiner and Applicants' undersigned representative, the Examiner stated that although he did not reject the claims for obviousness in view of Schmidt, *Medizinische Klinik*, 72(5), 144-160 (1975) ("Schmidt")[3], the Applicants should address this reference anyway, since the Examiner may want to use this reference in a future Office Action.

Applicants respectfully submit that Schmidt is merely a review article with no original data. While Schmidt relates to the administration of Aprotinin by inhalation, it cites to Rasche (discussed above) in support. See Ref. No. 82 in Schmidt. Schmidt also summarizes the prior clinical results, including those reported in Rasche, as follows: "Recent studies have shown that the disease process ***appears*** to be inhibited." However, a disclosure of inhibition of a disease process is ***not*** a disclosure of a use of a Kunitz domain serine protease inhibitor for accelerating the rate of mucociliary clearance as presently claimed. Further, Schmidt does not suggest an accelerated rate of mucociliary clearance by administering a composition comprising a Kunitz-type serine protease inhibitor. Accordingly Schmidt, either alone or in combination with another reference, cannot support an obviousness rejection.

[3] An English translation of Schmidt is enclosed with the accompanying Information Disclosure Statement.

Reconsideration and withdrawal of the rejections are respectfully requested. Should the Examiner believe that a discussion of this matter would be helpful, he is invited to telephone the undersigned at (312) 913-0001.

Respectfully submitted,

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APPENDIX A

1. (Currently amended) A method for accelerating the rate of mucociliary clearance in a subject with mucociliary dysfunction comprising administering to the subject an effective mucociliary clearance stimulatory amount of a composition comprising a Kunitz-type serine protease inhibitor and a physiologically acceptable carrier.

2. (Original) The method according to claim 1, wherein the composition is administered to the lung airways.

3. (Original) The method according to claim 1, wherein said composition is administered directly by aerosolization.

4. (Original) The method according to claim 1, wherein said composition is administered directly as an aerosol suspension into the mammal's respiratory tract.

5. (Original) The method according to claim 4, wherein said aerosol suspension includes respirable particles ranging in size from about 1 to about 10 microns.

6. (Original) The method according to claim 4, wherein said aerosol suspension includes respirable particles ranging in size from about 1 to about 5 microns.

7. (Original) The method according to claim 4, wherein said aerosol suspension is delivered to said subject by a pressure driven nebulizer.

8. (Original) The method according to claim 4, wherein said aerosol suspension is delivered to said subject by an ultrasonic nebulizer.

9. (Original) The method according to claim 4, wherein said aerosol suspension is delivered to said subject by a non-toxic propellant.

10. (Original) The method according to claim 1, wherein said carrier is a member selected from the group consisting of a buffered solution, an isotonic saline, normal saline, and combinations thereof.

11. (Original) The method according to claim 1 wherein the Kunitz-type serine protease inhibitor is aprotinin.

12. (Currently amended) The method according to claim 1, wherein the Kunitz-type serine protease inhibitor comprises the amino acid sequence: (SEQ ID NO.: 49).

13. (Currently amended) The method according to claim 1, wherein the Kunitz-type serine protease inhibitor comprises the amino acid sequence: (SEQ ID NO.: 2), (SEQ ID NO.: 45), (SEQ ID NO.: 47), (SEQ ID NO.: 70), or (SEQ ID NO.: 71).

14. (Currently amended) The method according to claim 1, wherein the Kunitz-type serine protease inhibitor comprises the amino acid sequence: (SEQ ID NO.: 4), (SEQ ID NO.: 5), (SEQ ID NO.: 6), (SEQ ID NO.: 7), (SEQ ID NO.: 3), (SEQ ID NO.: 50), (SEQ ID NO.: 1), or (SEQ ID NO.: 52).

15. (Currently amended) The method according to claim 1, wherein the Kunitz-type serine protease inhibitor comprises the amino acid sequence: (SEQ ID NO.: 8).

16. (Original) The method according to claims 12, 13, 14 or 15, wherein the Kunitz-type serine protease inhibitor is glycosylated.

17. (Original) The method according to claims 12, 13, 14 or 15, wherein the Kunitz-type serine protease inhibitor contains at least one intra-chain cysteine-cysteine disulfide bond.

18. (Currently amended) The method according to claims 12, 13, 14, or 15, wherein the Kunitz-type serine protease inhibitor contains at least one intra-chain cysteine-cysteine disulfide bond selected from the cysteine-cysteine paired groups consisting of CYS11-CYS61,

CYS20-CYS44, CYS36-CYS57, CYS106-CYS156, CYS115-CYS139, and CYS131-CYS152, wherein the cysteine residues are numbered according to the amino acid sequence of SEQ ID NO.: 52.